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Morales, Daniel R.; Dreischulte, Tobias; Lipworth, Brian J.; Donnan, Peter T.; Jackson, Cathy; Guthrie, Bruce

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Respiratory effect of beta-blocker eye drops in asthma: population based study and meta-analysis of clinical trials

Daniel R. Morales PhD. Quality, Safety & Informatics Group, Population Health Sciences, School of Medicine, University of Dundee, UK

Tobias Dreischulte PhD. NHS Tayside Medicines Governance Unit, Dundee, UK

Brian J. Lipworth MD. Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, UK

Peter T. Donnan PhD. Dundee Epidemiology and Biostatistics Unit, Population Health Sciences, School of Medicine, University of Dundee, UK

Cathy Jackson MD. School of Medicine, University of Central Lancashire, UK

Bruce Guthrie PhD. Quality, Safety & Informatics Group, Population Health Sciences, School of Medicine, University of Dundee, UK

SHORT TITLE: Risk from beta-blocker eye drop exposure in asthma

CORRESPONDING AUTHOR

Dr Daniel R Morales, Quality, Safety & Informatics Group, Population Health Sciences, School of Medicine, University of Dundee, Mackenzie Building, Dundee, DD2 4BF, UK

TEL: +44-1382-383706 E-mail: d.r.z.morales@dundee.ac.uk, danielmorales@nhs.net

ABSTRACT

Background: The prevalence of beta-blocker eye drop prescribing and respiratory effect of ocular beta-blocker administration in people with asthma has been poorly quantified despite their potential for rapid systemic absorption.

Methods: We measured the prevalence of ocular beta-blocker prescribing in people with asthma and ocular hypertension, and a nested case-control study (NCCS) measuring the risk of moderate exacerbations (rescue steroids in primary care) and severe exacerbations (asthma hospitalisation) using linked data from the UK Clinical Practice Research Datalink. We then performed a systematic review and meta-analysis of clinical trials evaluating changes in lung function following ocular beta-blocker administration in people with asthma.

Results: From 2000-2012, the prevalence of non-selective and selective beta-blocker eye drop prescribing in people with asthma and ocular hypertension fell from 23.0% to 13.4% and from 10.5% to 0.9% respectively. In the NCCS, the relative incidence (IRR) of moderate exacerbations significantly increased with acute non-selective beta-blocker eye drop exposure (IRR 4.83, 95%CI 1.56-14.94) but not with chronic exposure. In the meta-analysis, acute non-selective beta-blocker eye drop exposure caused significant mean falls in FEV1 of -10.9% (95%CI -14.9 to -6.9), and falls in FEV1 of ≥20% affecting one in three. Corresponding values for selective beta-blockers in people sensitive to ocular non-selective beta-blockers was -6.3% (95%CI -11.7 to -0.8), and a non-significant increase in falls in FEV1 of ≥20%.

Conclusion: Non-selective beta-blocker eye drops significantly affect lung function and increase asthma morbidity but are still frequently prescribed to people with asthma and ocular hypertension despite safer agents being available.

What is already known on the subject

Beta-blocker eye drops may be absorbed into the systemic circulation but the prevalence of beta-blocker prescribing and impact on lung function and exacerbations in people with asthma has been poorly quantified.

What this paper adds

Acute non-selective beta-blocker eye drop exposure significantly affects lung function and increases asthma morbidity but are still frequently prescribed to people with asthma and ocular hypertension despite safer agents being available.

Key words: Asthma; beta-blocker; glaucoma.

INTRODUCTION

International guidelines recommend that beta-blockers are contraindicated in asthma over safety concerns regarding acute bronchoconstriction (1-3). This effect results from endogenous and exogenous catecholamine antagonism at the pulmonary beta2-adrenoceptor leading to unopposed cholinergic tone. However, beta-blockers are not uncommonly prescribed to people with asthma, in part because their risk has been poorly quantified. Although the respiratory effect of oral beta-blockers in people with asthma appears to vary according to selectivity, dose and individual susceptibility, less is known regarding the effect of beta-blocker eye drops that may be systemically absorbed (4).

Beta-blocker eye drops are effective therapy for managing ocular hypertension. They reduce aqueous humour production and intra-ocular pressure by antagonising ciliary body beta-adrenoceptors thereby preventing complications such as visual loss (5). As with oral agents, beta-blocker eye drops vary in their degree of beta1:beta2-adrenoceptor selectivity with betaxolol being the principal ocular selective beta-blocker in clinical use (6). Although applied topically, systemic absorption may occur via the nasolacrimal system or the conjunctiva, without undergoing first pass metabolism (7). Despite safety concerns, the respiratory effect of beta-blocker eye drops in asthma has been poorly quantified despite reports of asthma deaths associated with ocular administration (8). Oral beta-blockers have been reported to be prescribed to around 2.2% of adults with asthma annually but the prevalence of beta-blocker eye drop prescribing in people with asthma, and their subsequent effect on lung function and asthma morbidity remains uncertain (9).

The aim of this study was to: measure beta-blocker eye drop prescribing in people with asthma and ocular hypertension; quantify the risk of asthma morbidity from ocular beta-blocker exposure; and meta-analyse clinical trial data evaluating changes in lung function following beta-blocker eye drop administration in people with asthma.

METHOD

Data source and population for pharmacoepidemiological studies

Data were extracted from the UK Clinical Practice Research Datalink (CPRD) which contains electronic medical record (EMR) data from >5 million UK people (further details of the data source are contained in online supplement 1) (10-12). People with medically treated asthma *and* ocular hypertension were identified by Read Codes and prescriptions for asthma and ocular hypertension medicines. The cohort consisted of people ≥18 years present in CPRD between 01/01/2000 and 31/12/2011. Subjects were eligible if they: were permanently registered with a general practice for ≥1 year; were from HES linked practices; were defined by CPRD as being acceptable for use in research (meaning their data had met quality standards); had a Read Code for asthma and were issued one or more prescriptions for ocular hypertension medicines.

Cohort entry was defined as the first ocular hypertension prescription issued on or after: 01/01/2000; date of the first asthma medicine; date of the patient's 18th birthday; and before the date of the patient's 80th birthday. The cohort was followed until either of the following occurred: an asthma event (defined in the nested case control section below); deregistration from the general practice; one year following the last asthma medication (thereby censoring people with asthma that had resolved or was inactive); end of ocular hypertension medical treatment; or end of the study period (31/12/2011). Asthma medicines were defined as: inhaled short-acting beta2-agonists (SABA); inhaled corticosteroids (ICS); inhaled long-acting beta2-agonists (LABA); oral leukotriene antagonists; and oral methylxanthines (13). All patients were issued two or more prescriptions for asthma medication. Ocular hypertension medicines were defined as ocular: beta-blockers; carbonic anhydrase inhibitors; miotics; sympathomimetics; or prostaglandin analogues (14). End of ocular hypertension medical treatment was defined by the last prescription date for an ocular hypertension medicine (plus a 90 day grace period) when 180 days had passed without any subsequent prescription of an ocular antihypertensive.

Drug utilisation study

The quarterly prevalence of non-selective and selective beta-blocker eye drop prescribing was calculated between 01/01/2000 and 31/12/2011. The numerator consisted of the number of people issued ≥1 non-selective or selective beta-blocker eye drop prescription and the denominator the total number of people with active asthma and ocular hypertension in the cohort during the same quarter.

Nested case control study

Outcomes

A population-based retrospective cohort using a matched, nested case-control design was used to account for time-varying confounders and drug exposure (15). Two nested case control studies were performed evaluating, 1) moderate asthma exacerbations and, 2) severe asthma exacerbations. Severe asthma exacerbations were defined as a hospitalisation for asthma (defined by ICD codes for asthma as the primary reason for hospitalisation). Moderate asthma exacerbations were defined by receipt of rescue oral steroids in primary care, identified as oral prednisolone prescriptions lasting less than 2 weeks in duration using ≥5mg strength tablets (therefore people taking maintenance corticosteroids were excluded from this analysis). For each outcome, the date of the first asthma event was the index date for case subjects. Please see online supplement 1 for further details.

Controls

Up to four controls were randomly selected from the same population and matched to each case on age decile, gender and calendar year of cohort entry using incidence density sampling. The risk set date was the index date for cases. Four cases of severe asthma exacerbation (3.1%) and 18 moderate exacerbations (3.0%) were initially unmatched, but were later included matched on gender and calendar year of cohort entry only with sensitivity analysis performed excluding these cases.

Exposure

Exposure was measured by the presence or absence of beta-blocker eye drop prescriptions issued prior to the index date. Beta-blocker eye drop exposure was categorised into: current acute exposure (defined as a prescription issued in a 30 day risk window before the index date and no previous prescriptions issued in days 31-365 before the index date); current chronic exposure (defined as a prescription issued in a 30 day risk window before the index date and ≥1 previous prescription issued in days 31-365 before the index date); and no exposure when there was no prescription issued in the risk window prior to the index date.

Confounders

The analyses were adjusted for the following confounders as described in online supplement 1 namely: asthma medicines issued within 90 days of the index date (ICS; LABA; leukotriene antagonists; methylxanthines; oral steroids (for the severe asthma exacerbation analysis), and SABAs); ever hospitalised for asthma; respiratory tract infections (RTI); exact age; smoking status; body mass index (BMI); index of multiple deprivation; nasal polyps; Charlson comorbidity index; and attendance at a primary care asthma review within the previous year. Please see online supplement 1 for further details.

Nested case control study analysis

Chi-squared tests and analysis of variance (ANOVA) were used to determine significant differences between patient characteristics. Multiple imputation was used to impute missing data on height, weight and smoking status as described in online supplement 1 (16). Conditional logistic regression was used to compute odds ratios for the association between outcomes and ocular beta-blocker exposure. Using an incidence density sampling approach, odds ratios represented unbiased estimators of incidence rate ratios (IRR). Analysis was carried out using SPSS v21 and STATA v13.

Nested case control study sensitivity analyses

For the nested case-control study, sensitivity analysis was performed: excluding people hospitalised within the risk period (assessing for potential immeasurable time bias); excluding people over the age of 40 years who smoked (assessing for potential misclassification with COPD where beta-blockers may be better tolerated and risk underestimated); excluding cases not originally matched on age; adjusting for ICS categorised into high, moderate and low dose; adjusting for a history of animal, drug or food allergy; adjusting for other ocular antihypertensive use; using a 60 and 90 day risk window (to establish whether risk attenuated over time); and a complete case analysis. Finally, a self-controlled case series controlling for time-varying confounders was performed to further evaluate the risk of moderate asthma exacerbations with acute non-selective beta-blocker eye drop exposure to compare with the nested case-control study (17). Full details of the self-controlled case series approach are contained in the online supplement 2.

Systematic review and meta-analysis

A systematic review of MEDLINE, EMBASE and CENTRAL was conducted following standard Cochrane methodology identifying controlled clinical trials published through 1 May 2015 evaluating the respiratory effects of *acute* beta-blocker eye drop exposure in people with asthma. Data were independently extracted on: mean percentage change in FEV1 (reported as the mean difference, MD); number of people experiencing falls in FEV1 of ≥20% and respiratory symptoms (reported as the risk difference, RD). In studies which included mixed populations (asthma and COPD) only data for patients with asthma were included. For included studies, non-selective beta-blocker eye drops were evaluated in people with asthma never exposed to beta-blocker eye drops (with unknown clinical response), but selective beta-blocker eye drops (betaxolol) were only evaluated in people with asthma with demonstrated respiratory sensitivity to non-selective beta-blockers. A fixed-effect meta-analysis was undertaken in Review Manager (RevMan) v5.1 (Copenhagen: The Nordic

Cochrane Centre, The Cochrane Collaboration, 2011). Sensitivity analyses and risk of bias was assessed as described in online supplement 3, which contains further details of the systematic review process including methodology for calculating missing standard deviations (18, 19).

RESULTS

Drug utilisation study

The cohort consisted of 4865 people with active asthma and ocular hypertension (mean age 67.8 years, 55.8% women) during which 128 severe asthma exacerbations and 598 moderate asthma exacerbations were identified. During follow-up, 1128 people (23.2%) were issued 36300 non-selective beta-blocker eye drop prescriptions and 241 people (5.0%) were issued 5544 selective beta-blocker eye drop prescriptions. The quarterly prevalence of beta-blocker eye drop prescribing in adults with active asthma and ocular hypertension is presented in figure 1. The prevalence of non-selective beta-blocker eye drop prescribing fell from a high of 23.0% (95% CI 20.0-26.3) in the first quarter of 2000 to 13.4% (95% CI 11.9-15.0) in the last quarter of 2011. The most commonly prescribed non-selective beta-blocker eye drops were timolol followed by levobunolol, then carteolol. The prevalence of betaxolol fell from 10.5% (95% CI 8.4-13.0) in the first quarter of 2000 to only 0.9% (95% CI 0.6-1.5) in the last quarter of 2011.

Nested case control study

Characteristics of cases and controls are shown in table 1. As expected, cases generally had significantly higher use of asthma medication, with a greater proportion having previously been hospitalised for asthma and experiencing a RTI in the 90 days prior to the index date. Crude and adjusted incidence rate ratios for the association between beta-blocker eye drop exposure and asthma exacerbations are presented in table 2. Acute non-selective beta-blocker eye drop exposure was associated with a 4.8-fold increased relative incidence of moderate asthma exacerbations (IRR 4.83, 95%CI 1.56-14.94, P=0.006). Chronic beta-blocker eye drop exposure was not associated with a

significantly increased risk of moderate or severe asthma exacerbations. Risk of severe asthma exacerbations from new non-selective beta-blocker eye drop exposure, and risk of both outcomes from new selective beta-blocker eye drop exposure could not be quantified because of a lack of exposure. Following multivariable adjustment, the strongest risk factors for moderate asthma exacerbations among people with asthma and ocular hypertension included: having had a RTI within the previous 90 days, having previously been hospitalised for asthma, the number of SABA prescriptions issued within the previous 90 days, BMI and smoking status (table 3).

Sensitivity analyses and self-controlled case series

Sensitivity analyses were in keeping with the main findings with an increased relative incidence of moderate asthma exacerbations associated with acute non-selective beta-blocker eye drop exposure (online supplement 1, supplementary tables 1 and 2). The relative incidence of moderate asthma exacerbations fell with increasing risk window duration in keeping with a short-lived risk following acute exposure. The self-controlled case series assessing acute non-selective beta-blocker eye drop exposure produced consistent findings with a 3.7-fold increased risk of moderate asthma exacerbations within the first 30 days of initiation (IRR 3.69 (95%CI 1.53-8.94), P=0.004) (please see online supplement 2 for further details).

Systematic review and meta-analysis of clinical trials

Of 203 references identified, nine controlled clinical trials evaluating single-dose beta-blocker eye drop exposure in people with asthma were included (online supplement 3: supplementary figure 1; supplementary table 4) (20-28). Non-selective beta-blocker eye drops were evaluated in 55 adults (mean age 47 years, 46% male) and selective beta-blocker eye drops in 33 adults (mean age 45 years, 66% male). Timolol was the most commonly evaluated non-selective beta-blocker and betaxolol the only selective beta-blocker evaluated.

Non-selective beta-blocker eye drops in unselected people with asthma

Compared to control, acute non-selective beta-blocker eye drop exposure caused: a mean fall in FEV1 of -10.9% (95%CI -14.9 to -6.9; p<0.001) (figure 2); a significant increase in falls in FEV1 of ≥20% (risk difference 0.28, 95%CI 0.14 to 0.42; p<0.001) (online supplement 3: supplementary figure 2) with a number needed to harm of approximately one in three; and a non-significant increase in respiratory symptoms (risk difference 0.40, 95%CI -0.05 to 0.85; p=0.08).

Selective beta-blocker eye drops in people with asthma with non-selective beta-blocker sensitivity

Compared to control, acute selective beta-blocker eye drop exposure in people with asthma sensitive to non-selective beta-blocker eye drops caused: a mean fall in FEV1 from baseline of -6.3% (95%CI -11.7 to -0.8; p=0.03) (figure 2); a non-significant increase in falls in FEV1 of ≥20% (risk difference 0.17, 95%CI -0.05 to 0.40; p=0.70) (online supplement 3: supplementary figure 2); and a non-significant increase in respiratory symptoms (risk difference 0.27, 95% CI -0.06 to 0.61, p=0.11).

Sensitivity analyses

When FEV1 threshold was varied, non-selective beta-blocker eye drops caused a significant increase in falls in FEV1 of ≥15% (risk difference 0.34, 95%CI 0.19 to 0.49; p<0.001) equating to a number needed to harm of one in three (figure 3). Betaxolol eye drops in people with asthma sensitive to non-selective beta-blockers, caused a significant increase in falls in FEV1 of ≥15% (risk difference 0.35, 95%CI 0.11 to 0.59; p=0.005) equating to a number needed to harm of one in three in people with prior sensitivity or a number needed to harm of one in nine people unselected on the basis of prior response (figure 3). The risk difference for falls in FEV1 of ≥15% for betaxolol 1% was 0.41 (95%CI 0.15 to 0.67; p=0.002) compared to 0.15 (95%CI -0.22 to 0.53) for betaxolol 0.5%. Results from other sensitivity analyses were consistent with the main findings.

Risk of bias

No significant statistical heterogeneity was detected. Of the nine studies, five were non-randomised and two were unblinded at high risk of bias (online supplement 3: supplementary figure 3). No funnel plot asymmetry was found to suggest publication bias.

DISCUSSION

This study measured the prevalence of beta-blocker eye drop prescribing and the respiratory effect of beta-blocker eye drop exposure in people with asthma and ocular hypertension. Although beta-blocker eye drop prescribing fell over the study period, 14% of people with asthma and ocular hypertension were still being prescribed a non-selective beta-blocker at the end of follow-up demonstrating a population at risk. Betaxolol prescribing also fell during the study period and now appears to be infrequently prescribed in the UK despite its potentially better safety profile perhaps related to the increased availability of compound eye drop preparations containing non-selective beta-blockers that may be preferentially prescribed to reduce treatment burden (14).

The relative incidence of moderate asthma exacerbations was significantly increased within thirty days of new ocular non-selective beta-blocker use with similar results observed in the nested case-control study and the self-controlled case series. In contrast, no significant increase in asthma morbidity was observed with chronic exposure in the nested case control study. The lack of effect with chronic exposure may be due to attenuation of risk from beta2-adrenoceptor up-regulation with chronic dosing (as suggested by studies evaluating chronic oral beta-blocker exposure in asthma) or possibly survival bias whereby longer-term treatment is more likely to occur in people tolerating acute exposure (29). Several readily identifiable risk factors significantly associated with increased asthma severity or transient airway hyperresponsiveness were identified for moderate exacerbations which clinicians could use to better judge risk from non-selective beta-blocker

exposure. These included having had a recent or concomitant respiratory tract infection, a prior history of asthma hospitalisation, being a current smoker, increasing body mass index and SABA use.

The meta-analysis of controlled clinical trials demonstrated that acute exposure to non-selective beta-blocker eye drops caused significant mean falls in FEV1 of 10.9%, falls in FEV1 of ≥20% affecting approximately one in three and a non-significant increase in respiratory symptoms. For mean falls in FEV1, findings were similar to the effects of oral non-selective beta-blockers in people with asthma (4). However, the number of people experiencing falls in FEV1 of ≥20% following oral beta-blocker administration was smaller suggesting that non-selective beta-blocker eye drops may carry a greater risk.

Betaxolol administration in people sensitive to ocular non-selective beta-blockers caused only small significant mean falls in FEV1, and non-significant increases in falls in FEV1 of ≥20% and respiratory symptoms. However, smaller falls in FEV1 may still be clinically significant, and betaxolol caused significant falls in FEV1 of ≥15% with a number needed to harm equivalent to one in nine people with asthma unselected on the basis of prior response. Falls in FEV1 ≥15% following acute betaxolol exposure appeared to be significant for betaxolol 1% compared to betaxolol 0.5% suggesting a possible dose response relationship which has also be demonstrated with acute oral selective beta-blocker exposure (4).

The most commonly evaluated non-selective beta-blocker eye drop in our cohort was timolol which has greater selectivity for the beta2-adrenoceptor than other commonly used non-selective beta-blockers. In this regard, the absolute degree of beta2-adrenoceptor binding affinity (i.e. the equilibrium dissociation constant, Kd) shows a rank order of timolol>carvedilol>propranolol>nadolol>sotalol, potentially explaining the apparent greater risk following ocular administration potentiated by the lack of first pass liver metabolism and rapid

systemic absorption. This rapid systemic absorption has been compared to that of systemic exposure following intravenous beta-blocker administration in terms of beta2-adrenoceptor occupancy and cardiopulmonary effects (7). It is uncertain whether any patients in our cohort routinely performed lacrimal duct compression following beta-blocker eye drop administration which could potentially modify the risk of systemic absorption and therefore risk of exacerbation. Despite this, our findings suggest that acute non-selective beta-blocker eye drops cause significant changes in lung function in people with asthma and also increase asthma morbidity in the real world.

Strengths and limitations

A key strength of our study is that it combines pharmacoepidemiological analysis of linked routine health data supported by meta-analysis of clinical trial data, making it the most comprehensive evaluation on the risks of beta-blocker eye drops in people with asthma. However, our study has several limitations. First, it was not possible to comprehensively evaluate all types of ocular beta-blocker exposure in our nested case control study due to limited available data. Residual confounding from unmeasured covariates may also exist because data on lung function was not routinely available. However the self-controlled case series is a design in which the person acts as their own control and this produced consistent findings for acute non-selective beta-blocker exposure.

Exposure to oral steroids may conceivably induce or worsen ocular hypertension acting as a potential confounder by theoretically increasing the likelihood of treatment with beta-blocker eye drops. However, this is unlikely to have influenced our results for several reasons. First, the increased risk with non-selective beta-blocker eye drops was seen with moderate exacerbations were the outcome of interest consisted of *incident* rescue oral steroid use. Second, the distribution of ocular hypertensive medication use among cases and controls is similar suggesting no significant

difference in the severity of ocular hypertension between groups. Lastly, sensitivity analysis additionally adjusting for ocular antihypertensive use produced consistent results.

The nested case control study outcomes relied upon accurate electronic prescribing and discharge coding and potentially not all outcomes were identified. Nevertheless, hospital discharges are routinely recorded in the UK and almost all chronic community prescriptions are issued electronically from general practice, including most drugs recommended by specialists. Limitations of our meta-analysis include the small number of participants, the potential risk of bias from non-randomised or unblinded studies and the use of FEV1 which may be less sensitive than other methods at measuring airway resistance such as impulse oscillometry (31). Despite these limitations, results were generally consistent between study designs and were similar to a previous meta-analysis evaluating oral beta-blockers in asthma (4).

In conclusion, initiating treatment with non-selective beta-blocker eye drops causes significant changes in lung function in people with asthma and ocular hypertension, and is associated with increased asthma morbidity in the real world. Nevertheless, people with asthma and ocular hypertension are still frequently prescribed non-selective beta-blocker eye drops whilst safer selective agents are infrequently prescribed. These findings support recommendations that non-selective beta-blocker eye drops should be avoided in people with asthma and ocular hypertension.

AUTHOR CONTRIBUTIONS

DM conceived the idea. DM and TD reviewed the literature and extracted the data for the systematic review and meta-analysis. All authors contributed to the study design and interpretation of the findings. DM analysed the data and is guarantor of the data. All authors contributed to the drafting of the manuscript and approved the final draft.

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Table 1. Characteristics of cases and controls in the nested case control study.

Characteristics	Severe exacerbation Number (%)		Moderate exacerbation Number (%)	
	Cases N=128	Controls N=489	Cases N=598	Controls N=2196
Age (years, SD) ¥	70.0 (12.3)	73.0 (9.6)	70.3 (10.5)*	71.6 (8.9)
Female gender	85 (66.4)	328 (67.1)	85 (66.4)	328 (67.1)
Years of follow-up (SD) ¥	2.4 (2.6)	2.4 (2.6)	1.6 (2.2)	1.5 (2.1)
Asthma therapy				
-ICS	57 (44.5)	235 (48.1)	266 (44.5)	1022 (46.5)
-LABA	36 (28.1)*	66 (13.5)	72 (12.0)	213 (9.7)
-LABAICS	43 (33.6)	141 (28.8)	185 (30.9)*	560 (25.5)
-Leukotriene antagonist	15 (11.7)	22 (4.5)	23 (3.8)*	28 (1.3)
-Methylxanthine	24 (18.8)	51 (10.4)	28 (4.7)	90 (4.1)
-Oral steroid	72 (56.3)*	84 (17.2)	n/a	n/a
-No. of SABA prescriptions (SD) ¥	3.0 (2.5)*	1.7 (1.6)	1.6 (1.6)*	1.2 (1.4)
Ocular hypertension therapy				
-Non-selective beta-blocker	15 (11.7)	75 (15.3)	84 (14.0)	303 (13.8)
-Selective beta-blocker	5 (3.9)	10 (2.0)	15 (2.5)	77 (3.5)
-Prostaglandin analogue	84 (65.6)	349 (71.4)	441 (73.7)	1598 (72.8)
-Carbonic anhydrase inhibitor	45 (35.2)	131 (26.8)	161 (26.9)	618 (28.1)
-Sympathomimetic	12 (16.4)	67 (13.7)	48 (8.0)	207 (9.4)
-Miotic	5 (3.9)	20 (4.1)	34 (5.7)	89 (4.1)
Comorbidity				
-Nasal polyps	9 (7.0)	24 (4.9)	23 (3.8)	99 (4.5)
-BMI (SD) ¥	27.4 (5.7)	27.3 (5.3)	28.2 (5.4)*	27.4 (6.1)
-Charlson comorbidity index (SD) ¥	2.7 (2.0)	2.5 (1.9)	2.4 (1.8)	2.5 (1.9)
Smoking status				
-Current smoker	13 (10.2)	82 (16.8)	100 (16.7)*	229 (10.4)
-Ex-smoker	66 (51.6)	258 (52.8)	310 (51.8)	1131 (51.5)
-Non-smoker	39 (30.5)	129 (26.4)	169 (28.3)	709 (32.3)
-Missing	10 (7.8)	20 (4.1)	19 (3.2)	127 (5.8)
Primary care asthma review	51 (39.8)	151 (30.9)	253 (42.3)	882 (40.2)
Previous asthma hospitalisation	32 (25.0)*	20 (4.1)	30 (5.0)*	47 (2.1)
RTI 90 days prior to index date	29 (22.7)*	50 (10.2)	89 (14.9)*	129 (5.9)

¥Continuous variables analysed with ANOVA, otherwise categorical variable analysed using Chi-square test.

*Characteristics with statistically significant differences between cases and controls (p-value < 0.05).

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Severe exacerbation = asthma hospitalisation. Moderate exacerbation = receipt of rescue oral steroid in primary care.

Table 2. Crude and adjusted incidence rate ratios (IRR) for the association between beta-blocker eye drop exposure and asthma exacerbations in the nested case control study.

	Any exposure				Acute exposure				Chronic exposure			
	Crude	Adjusted			Crude	Adjusted			Crude	Adjusted		
	IRR	IRR	95% CI	p-value	IRR	IRR	95% CI	p-value	IRR	IRR	95% CI	p-value
Non-selective beta-blocker												
▪ Severe exacerbation	0.97	1.08	0.48-2.42	0.860	-	-	-	-	1.04	1.10	0.49-2.49	0.818
▪ Moderate exacerbation	1.16	1.21	0.89-1.66	0.224	4.01	4.83	1.56-14.94	0.006	1.06	1.11	0.81-1.54	0.517
Selective beta-blocker												
▪ Severe exacerbation	1.85	1.85	0.32-10.88	0.496	-	-	-	-	1.85	1.85	0.32-10.89	0.494
▪ Moderate exacerbation	0.85	0.98	0.47-2.02	0.945	-	-	-	-	0.85	0.97	0.47-2.01	0.941

Severe exacerbation = asthma hospitalisation. Moderate exacerbation = receipt of rescue oral steroid in primary care.
Empty cells = unable to estimate due to lack of exposure in the risk window.

Table 3. Characteristics associated with risk of moderate asthma exacerbations among people with asthma and ocular hypertension.

Characteristic	Primary care asthma exacerbation		
	Crude IRR (95%CI)	Adjusted IRR (95%CI)	p-value
RTI within the last 90 days	2.85 (2.12-3.82)	2.93 (2.14-4.00)	0.001
Past asthma hospitalisation	2.93 (1.81-4.70)	2.10 (1.25-3.53)	0.001
Smoker	1.86 (1.37-2.54)	1.72 (1.22-2.42)	0.002
SABA prescription*	1.20 (1.13-1.28)	1.17 (1.10-1.25)	0.001
BMI¥	1.02 (1.01-1.04)	1.03 (1.01-1.05)	0.002

* Per additional SABA prescription in the previous 90 days (continuous variable).

¥ Per unit increase in BMI (continuous variable). Other variables are categorical variables.

FIGURES

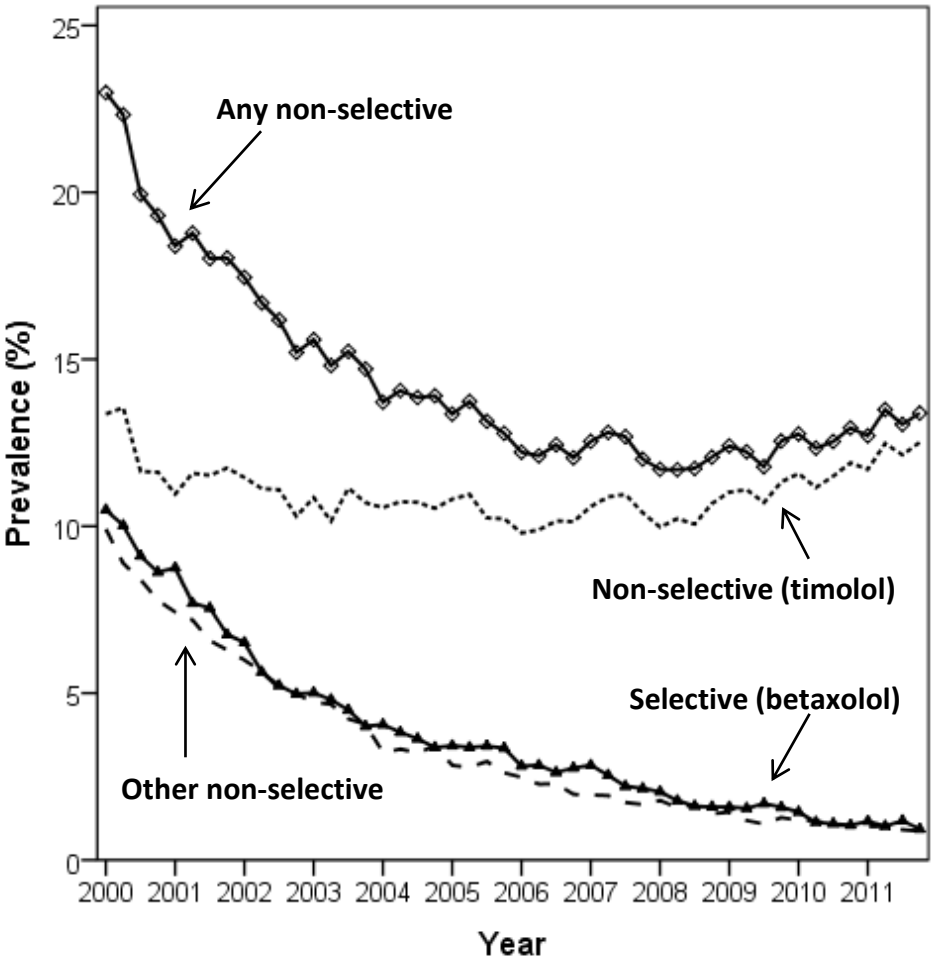


Figure 1. Prevalence of beta-blocker eye drop prescribing among people with active asthma and ocular hypertension.

Any non-selective beta-blocker

Timolol

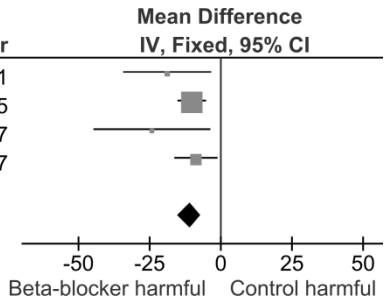
Selective beta blockers (betaxolol)

Other non-selective beta-blocker (levobunolol, carteolol, metipranolol)

a) Acute non-selective beta-blocker eye drop exposure in people with no prior exposure

Study or Subgroup	Beta-blocker Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Vonwil 1981	-19.74	16.13	5	-0.9	7.22	5	6.6%	-18.84 [-34.33, -3.35]	1981
Hugues 1985	-11.4	9.3	15	-1.2	3.49	15	62.4%	-10.20 [-15.23, -5.17]	1985
Bohm 1987	-25	16.58	5	-0.79	16.58	5	3.7%	-24.21 [-44.76, -3.66]	1987
Hugues 1987	-9.35	16.77	20	-0.6	4.47	20	27.3%	-8.75 [-16.36, -1.14]	1987
Total (95% CI)			**45**			**45**	**100.0%**	**-10.90 [-14.87, -6.92]**	

Heterogeneity: Chi² = 3.00, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 5.38 (P < 0.00001)



b) Acute selective beta-blocker exposure in people with prior sensitivity to non-selective eye drops

Study or Subgroup	Beta-blocker Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schoene 1984	-15.98	17.38	9	-9	15.92	9	12.7%	-6.98 [-22.38, 8.42]
Dunn 1986	-8.66	11.34	8	-0.79	11.34	8	24.3%	-7.87 [-18.98, 3.24]
Bleckman 1987	-0.2	4.75	10	5.05	11.89	10	47.7%	-5.25 [-13.19, 2.69]
Schoene 1992	-1.47	10.03	4	4.72	10.19	4	15.3%	-6.19 [-20.20, 7.82]
Total (95% CI)			**31**			**31**	**100.0%**	**-6.25 [-11.73, -0.77]**

Heterogeneity: Chi² = 0.15, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.03)

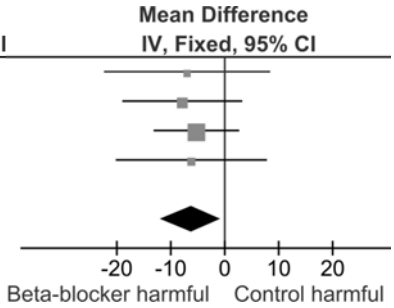
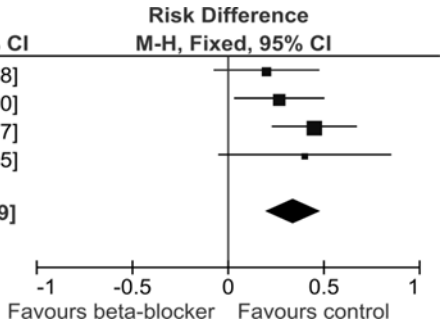


Figure 2: Mean change in FEV1 following acute beta-blocker eye drop exposure.

a) Acute non-selective beta-blocker eye drops in people with no prior exposure

Study or Subgroup	Beta-blocker Events	Beta-blocker Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bohm 1987	2	10	0	10	20.0%	0.20 [-0.08, 0.48]
Hugues 1985	4	15	0	15	30.0%	0.27 [0.03, 0.50]
Hugues 1987	9	20	0	20	40.0%	0.45 [0.23, 0.67]
Vonwil 1981	2	5	0	5	10.0%	0.40 [-0.05, 0.85]
Total (95% CI)		**50**		**50**	**100.0%**	**0.34 [0.19, 0.49]**
Total events	17		0			

Heterogeneity: Chi² = 2.36, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)



b) Acute selective beta-blocker exposure in people with prior sensitivity to non-selective eye drops

Study or Subgroup	Beta-blocker Events	Beta-blocker Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Schoene 1984	5	9	1	9	39.1%	0.44 [0.06, 0.83]	1984
Dunn 1986	3	8	0	8	34.8%	0.38 [0.02, 0.73]	1986
De Vos 1989	0	2	0	2	8.7%	0.00 [-0.60, 0.60]	1989
Schoene 1992	1	4	0	4	17.4%	0.25 [-0.23, 0.73]	1992
Total (95% CI)		**23**		**23**	**100.0%**	**0.35 [0.11, 0.59]**	
Total events	9		1				

Heterogeneity: Chi² = 1.73, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)

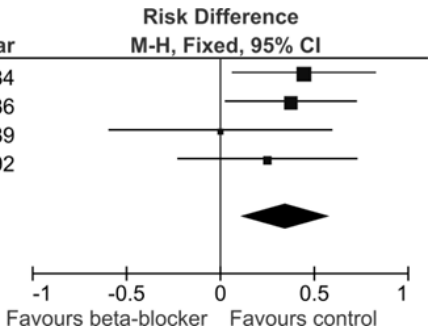


Figure 3: Falls in FEV1 of 15% or greater following acute beta-blocker eye drop exposure.

ONLINE SUPPLEMENT 1: BETA-BLOCKER EYE DROPS IN ASTHMA

PHARMACOEPIDEMIOLOGYICAL STUDY SUPPLEMENTARY METHODS

Further details on data source

The UK Clinical Practice Research Datalink (CPRD) contains linked health data about patient demographics, prescriptions, diagnoses, hospitalizations and deaths. Diagnoses within CPRD are recorded using Read Codes, a hierarchical thesaurus of coded clinical terms used in UK primary care (10). Approximately 60% of general practices in CPRD are linked to the Hospital Episode Statistics (HES) database, containing details of admissions to NHS hospitals in England. HES diagnoses are recorded using the International Classification of Disease (ICD10) coding system. General practices and patients within CPRD are required to meet defined quality standards in order to contribute data. Diagnoses within CPRD have high validity with a positive predictive value for respiratory disease and glaucoma of around 90% (11, 12). The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (and is part of protocol 12_061R3). The observational studies are reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) requirements.

Further details on population and outcomes used in the nested case control analysis

The study population was restricted to people with asthma and ocular hypertension so that controls were sampled from a more representative population. Severe exacerbations were defined as a hospitalisation for asthma identified by the following ICD codes: J45.0, J45.1, J45.8, J45.9, J46, 493, 493.0, 493.1, 493.9. Moderate exacerbations were defined by receipt of rescue oral steroids defined as oral prednisolone prescriptions lasting less than 2 weeks in duration using ≥5mg strength tablets. People with non-rescue oral steroids were excluded from the moderate exacerbation analysis to prevent outcome misclassification bias. Asthma death was not evaluated as an outcome due to lack of power.

Further details on confounders assessed in the nested case control analysis

To account for differences in asthma severity, prescriptions issued within 90 days of the index date were modelled as categorical exposure indicators (ICS, LABA, leukotriene antagonists, methylxanthines, oral steroids) and as continuous exposure indicators (total number of SABA prescriptions issued within 90 days of the index date). Additional risk adjustment was performed for: ever hospitalised for asthma; respiratory tract infection (RTI) within 90 days of the index date; nasal polyps; attendance at a primary care asthma review within the previous year (categorical variables); smoking status (categorised into current, ex-smoker, never smoked); exact age; body mass index (BMI); index of multiple deprivation; Charlson comorbidity index (continuous variables).

Sensitivity analysis was performed evaluating the effect of adjusting for ICS dose within the risk window. All doses of ICS were converted to fluticasone-equivalent doses based on their relative topical potency (1). Dose equivalencies used were beclomethasone 100 μg, budesonide 100 μg, fluticasone 50 μg, clenil 100 μg, ciclesonide 50 μg, mometasone 50 μg. The converted doses were categorised as high (fluticasone ≥1000 μg/day), moderate (500–999 μg/day) and low (< 500 μg/day). Sensitivity analysis was also performed modelling a history of animal, drug or food allergy recorded in the primary care medical record before the index date.

Further details on multiple imputation used in the nested case control analysis

Multiple imputation was used to impute missing data on height, weight and smoking status assuming data was missing at random. The imputation model included all variables relating to clinical characteristics, asthma events, asthma medication and beta-blocker eye drop exposure. Multiple imputation was carried out using fully conditional specification, with linear regression for continuous variables and logistic regression for categorical variables using five cycles analysed using Rubin's rules (16).

PHARMACOEPIDEMIOLOGYICAL STUDY SUPPLEMENTARY RESULTS

Supplementary table 1. Sensitivity analyses for non-selective beta-blocker eye drop use and asthma events.

	Any exposure		Incident exposure		Prevalent exposure	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Adjusting for other ocular hypertensives						
▪ Severe exacerbation	0.96	0.42-2.23	-	-	0.98	0.42-2.28
▪ Moderate exacerbation	1.26	0.92-1.73	5.08	1.65-15.70	1.14	0.82-1.59
ICS modelled by dose						
▪ Severe exacerbation	0.87	0.39-1.94	-	-	0.89	0.40-1.97
▪ Moderate exacerbation	1.24	0.90-1.69	4.78	1.54-14.83	1.13	0.81-1.56
Adjusted for allergies						
▪ Severe exacerbation	0.97	0.44-2.14	-	-	0.99	0.45-2.18
▪ Moderate exacerbation	1.21	0.89-1.65	4.82	1.55-14.97	1.10	0.80-1.52
Hospitalised in risk window						
▪ Severe exacerbation	1.22	0.52-2.87	-	-	1.26	0.53-2.97
▪ Moderate exacerbation	1.24	0.89-1.72	4.55	1.46-14.13	1.12	0.79-1.57
Smokers over 40 years						
▪ Severe exacerbation	0.88	0.35-2.18	-	-	0.90	0.36-2.23
▪ Moderate exacerbation	1.13	0.79-1.60	3.98	1.12-14.11	1.04	0.72-1.49
Unmatched on age						
▪ Severe exacerbation	1.09	0.48-2.45	-	-	1.11	0.49-2.50
▪ Moderate exacerbation	1.18	0.86-1.62	4.81	1.56-14.79	1.07	0.77-1.49
Complete case analysis						
▪ Severe exacerbation	1.25	0.52-3.02	-	-	1.29	0.53-3.12
▪ Moderate exacerbation	1.19	0.85-1.65	7.77	2.23-27.09	1.06	0.75-1.49
60 days risk window						
▪ Severe exacerbation	0.81	0.38-1.71	-	-	0.85	0.40-1.80
▪ Moderate exacerbation	1.12	0.84-1.49	1.96	0.85-4.75	1.06	0.79-1.43
90 day risk window						
▪ Severe exacerbation	1.00	0.49-2.02	-	-	1.08	0.53-11.56
▪ Moderate exacerbation	1.10	0.83-1.45	1.61	0.74-3.50	1.05	0.78-1.40

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; cases unmatched on age; and a complete case analysis; varying risk window duration. IRR=incidence rate ratio. Adjusted results presented. Severe exacerbations = asthma hospitalisation. Moderate exacerbation = receipt of rescue oral steroids in primary care. Other ocular hypertensives = carbonic anhydrase inhibitors, prostaglandin analogues, miotics and sympathomimetics.

Supplementary table 2. Sensitivity analyses for selective beta-blocker eye drop use and asthma events.

	Any exposure		Incident exposure		Prevalent exposure	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Adjusting for other ocular hypertensives						
▪ Severe exacerbation	1.59	0.26-9.70	-	-	1.59	0.26-9.70
▪ Moderate exacerbation	0.99	0.47-2.05	-	-	0.97	0.47-2.02
ICS by dose						
▪ Severe exacerbation	1.30	0.25-6.77	-	-	1.31	0.25-6.76
▪ Moderate exacerbation	0.96	0.47-2.00	-	-	0.96	0.46-1.98
Adjusted for allergies						
▪ Severe exacerbation	1.46	0.30-7.12	-	-	1.47	0.30-7.12
▪ Moderate exacerbation	0.98	0.48-2.03	-	-	0.98	0.47-2.02
Hospitalised in risk window						
▪ Severe exacerbation	1.66	0.27-10.21	-	-	1.67	0.27-10.21
▪ Moderate exacerbation	1.03	0.50-2.14	-	-	1.02	0.49-2.13
Smokers over 40 years						
▪ Severe exacerbation	0.89	0.09-8.55	-	-	0.89	0.09-8.57
▪ Moderate exacerbation	0.94	0.38-2.36	-	-	0.94	0.38-2.36
Unmatched on age						
▪ Severe exacerbation	1.94	0.33-11.55	-	-	1.94	0.33-11.53
▪ Moderate exacerbation	0.99	0.48-2.06	-	-	0.98	0.47-2.04
Complete case analysis						
▪ Severe exacerbation	2.64	0.33-21.23	-	-	2.63	0.33-21.11
▪ Moderate exacerbation	0.98	0.46-2.08	-	-	0.98	0.46-2.08
60 day risk window						
▪ Severe exacerbation	1.87	0.32-11.07	-	-	1.88	0.32-11.10
▪ Moderate exacerbation	0.82	0.45-1.51	-	-	0.85	0.46-1.57
90 day risk window						
▪ Severe exacerbation	2.88	0.72-11.56	-	-	2.87	0.71-11.56
▪ Moderate exacerbation	0.81	0.45-1.47	-	-	0.86	0.47-1.55

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; cases unmatched on age; and a complete case analysis; varying risk window duration. IRR=incidence rate ratio. Adjusted results presented. Severe exacerbations = asthma hospitalisation. Moderate exacerbation = receipt of rescue oral steroids in primary care. Other ocular hypertensives = carbonic anhydrase inhibitors, prostaglandin analogues, miotics and sympathomimetics.

ONLINE SUPPLEMENT 2: BETA-BLOCKERS EYE DROPS IN ASTHMA

SELF-CONTROLLED CASE SERIES SUPPLEMENTARY METHOD

Self-controlled case series study and risk periods

A secondary analysis evaluating risk of moderate exacerbations with acute non-selective beta-blocker eye drop exposure was performed using a case-exposure self-controlled case series (SCCS). For this analysis a 360 day observation period was used commencing 180 days prior to incident non-selective beta-blocker eye drop prescription (defined as the first prescription in people with at least 1 year's follow-up prior to receipt). A 30 day pre-risk period was excluded from the analysis to account for event-dependent exposures (17). Oral steroid prescriptions issued within eight days of each other were considered the same moderate exacerbation event. A 30 day acute risk period commencing from the date of the incident prescription was used to allow comparison with the nested case control study. Exposure beyond the 30 day acute risk period was defined as chronic exposure. End of exposure was determined as 30 days following the date of the last non-selective beta-blocker eye drop prescription.

Self-controlled case series confounder adjustment and data analysis

The SCCS controls for time-fixed confounding. To control for time-varying confounding, the observation period was restricted to 360 days and adjustment made for the following time-varying exposures: ICS; LABAs; leukotriene antagonists; methlyxanthines; total number of SABA prescriptions; and seasonal variation. Age was not a significant time-varying confounder in this analysis because of the short study period. The duration of any hospitalizations occurring during the study period were calculated and this person time subtracted from each corresponding exposure group to prevent immeasurable time bias. The SCCS was analysed using conditional Poisson regression producing IRRs and 95% confidence intervals (17).

SELF-CONTROLLED CASE SERIES SUPPLEMENTARY RESULTS

The risk of moderate asthma exacerbations with acute beta-blocker eye drop exposure was evaluated in 26 eligible people (mean age 66 years, 53.8% women) initiating non-selective beta-blocker eye drops who experienced 48 moderate exacerbations during the observation period (supplementary table 3). Non-selective beta-blocker eye drops were associated with a 3.7-fold increased risk of moderate asthma exacerbation within the first 30 days of initiation (IRR 3.69, 95%CI 1.53-8.94, P=0.004).

Supplementary table 3. Incidence rate ratios for non-selective beta-blocker eye drop exposure and moderate asthma exacerbations in the self-controlled case series.

Risk Period	Person time (Days)	Events	Crude IRR	Adjusted IRR	Adjusted 95%CI	p-value
Baseline	4724	18	1.00	Reference	-	-
Pre-risk	769	2	0.66	0.67	0.15-2.97	0.596
Acute	766	11	3.63	3.69	1.53-8.94	0.004
Chronic	3030	17	1.38	1.24	0.52-2.94	0.630

IRR = incidence rate ratios for a 30 day acute risk period.

ONLINE SUPPLEMENT 3: BETA-BLOCKER EYE DROPS IN ASTHMA

SYSTEMATIC REVIEW AND META-ANALYSIS SUPPLEMENTARY METHODS

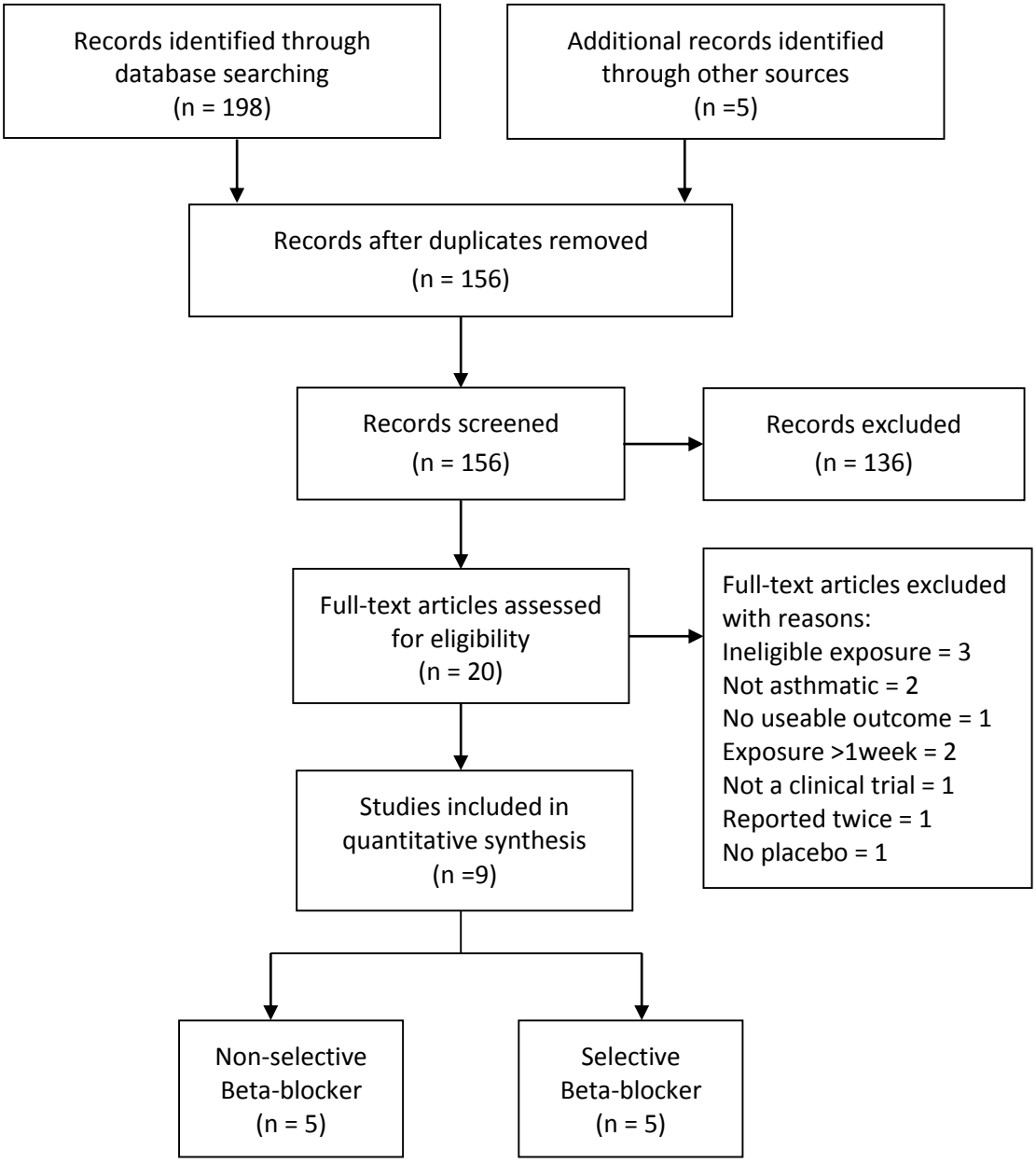
A systematic review of MEDLINE, EMBASE and CENTRAL databases was conducted following standard Cochrane methodology using a pre-specified protocol and search strategy to identify all controlled clinical trials published through 1 May 2015 evaluating the respiratory effects of acute beta-blocker eye drop exposure in people with asthma. Study selection was performed independently by two reviewers (DM and TD). Full texts were obtained for articles considered of relevance, and independently appraised by the reviewers with inclusion based on consensus. Manual searches from reference lists of included studies were performed to identify additional trials. Eligibility was not restricted by language of publication or by trial design. Only published data from trials were included in the meta-analysis. Methodological quality and risk of bias for each trial were evaluated using the Cochrane Collaboration tool for assessing risk of bias (18). Publication bias was assessed by visually examining funnel plots for asymmetry. The systematic review was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews) requirements.

Meta-analysis sensitivity analyses

For the meta-analysis, sensitivity analysis was conducted using falls in FEV1 of ≥15% because smaller falls in FEV1 may still be clinically significant. Missing standard deviations were calculated using individual patient data were available and from p-values using the method described by Elbourne et al. (19). For remaining missing values, the median p-value was imputed and sensitivity analyses performed using the minimum and maximum p-values to ensure conclusions remained consistent. All changes in FEV1 were calculated relative to baseline levels.

SYSTEMATIC REVIEW AND META-ANALYSIS SUPPLEMENTARY RESULTS

Supplementary figure 1: PRISMA flow diagram for the systematic review study selection



Supplementary table 4. Characteristics of included studies for the systematic review and meta-analysis.

Study (reference)	Number of asthmatic patients	Trial randomized	Trial blinded	Ocular beta-blocker (concentration)
Bleckmann 1987[20]	10	Yes	Yes	Betaxolol (0.5%)*
Bohm 1987[21]	15	Yes	Yes	Timolol (0.5%), Metipranolol (0.6%), Pindolol (1%)
De Vos 1989[22]	2	No	Yes	Betaxolol (0.5%)*
Dunn 1986[23]	8	No	Yes	Betaxolol (1%)*
Hugues 1985[24]	15	No	No	Timolol (0.25-0.5%)
Hugues 1987[25]	20	No	No	Carteolol (1-2%), Metipranolol (0.3-0.6%)
Schoene 1984[26]	9	Yes	Yes	Betaxolol (1%)*
Schoene 1992[27]	4	No	Yes	Betaxolol (0.5%)*
Vonwil 1981[28]	5	Yes	Yes	Timolol (0.5%)

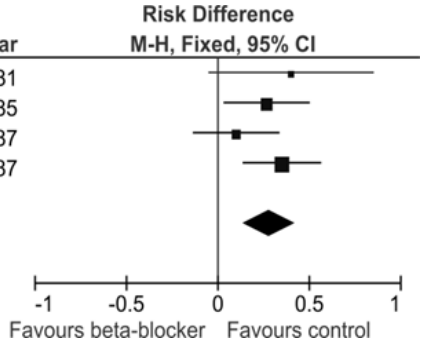
*Selective beta-blocker. Only data from patients with asthma extracted from eligible studies.

Supplementary figure 2: Fall in FEV1 of 20% or greater following acute beta-blocker eye drop exposure.

a) Acute non-selective beta-blocker eye drops in people with no prior exposure

Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Vonwil 1981	2	5	0	5	10.0%	0.40 [-0.05, 0.85]	1981
Hugues 1985	4	15	0	15	30.0%	0.27 [0.03, 0.50]	1985
Bohm 1987	1	10	0	10	20.0%	0.10 [-0.14, 0.34]	1987
Hugues 1987	7	20	0	20	40.0%	0.35 [0.13, 0.57]	1987
Total (95% CI)		**50**		**50**	**100.0%**	**0.28 [0.14, 0.42]**	
Total events	14		0				

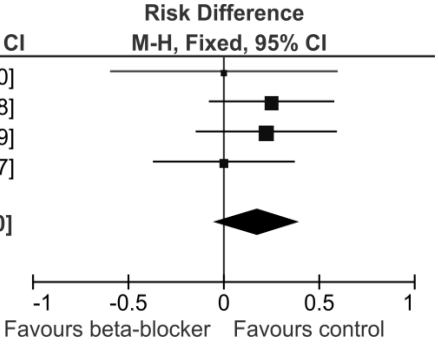
Heterogeneity: Chi² = 2.90, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 3.93 (P < 0.0001)



b) Acute selective beta-blocker exposure in people with prior sensitivity to non-selective eye drops

Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
De Vos 1989	0	2	0	2	8.7%	0.00 [-0.60, 0.60]
Dunn 1986	2	8	0	8	34.8%	0.25 [-0.08, 0.58]
Schoene 1984	3	9	1	9	39.1%	0.22 [-0.15, 0.59]
Schoene 1992	0	4	0	4	17.4%	0.00 [-0.37, 0.37]
Total (95% CI)		**23**		**23**	**100.0%**	**0.17 [-0.05, 0.40]**
Total events	5		1			

Heterogeneity: Chi² = 1.44, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)



Risk of bias from included clinical trials

No significant statistical heterogeneity was detected. Of the nine included studies, five were non-randomised and two were unblinded at high risk of bias (supplementary figure 4). No funnel plot asymmetry was found to suggest publication bias.

Supplementary figure 4. Cochrane collaboration tool for assessing risk of bias among included studies.